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# Identifying the germline variation spectrum and predisposition genes in Chinese ovarian cancer using whole exome sequencing

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## Abstract

**Background** Next-generation sequencing (NGS) allows for the simultaneous sequencing of multiple cancer predisposition genes. We assessed the frequency and spectrum of germline variations in individuals with ovarian cancer (OC), using whole exome sequencing (WES).

**Methods** A total of 92 patients with OC, with or without a family history of cancer, were consecutively recruited between May 2020 and September 2023. Germline DNA was sequenced using WES.

**Results** Among the 12 canonical OC predisposition genes recommended by the National Comprehensive Cancer Network (NCCN) guidelines, 26 patients (28.26%) were found to have 28 pathogenic or likely pathogenic variations in 5 genes, including *BRCA1* ($n=13$), *BRCA2* ($n=8$), *RAD51D* ($n=4$), *BRIP1* ($n=2$), and *MSH2* ($n=1$). Additionally, 24 patients (26.08%) harbored variants of uncertain significance (VUS) in canonical OC predisposition genes or other putative OC predisposition genes, including 3 loss of function variation: NM_001142548.1(*RAD54L*): c.1825C>T (p.Arg609Ter), NM_002907.3(*RECQL*): c.796C>T (p.Gln266Ter), and NM_001114132.2 (*NBEAL1*): c.5837dup (p.Tyr1946Ter). Moreover, we found that the detection rate of predisposition genes was correlated with a family history of malignancies and a personal history of other malignancies.

**Conclusions** Using WES, we found that 28.26% of patients with OC had germline cancer-predisposing variations. WES substantially improved the detection rates of a wide spectrum of variations in OC patients and uncovered putative predisposition genes.

**Keywords** Ovarian cancer, Germline variation, Next-generation sequencing, Predisposition genes

## Introduction

OC originates from the ovary, fallopian tube, and peritoneum, ranking fifth among female cancers with about 320,000 new cases and 200,000 deaths annually [1, 2]. The most common type is epithelial ovarian cancer (EOC), which constitutes around 90% of cases and includes five main subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), mucinous carcinoma (MC), endometrioid carcinoma (ENC), and clear cell carcinoma (CCC) [3, 4].

OC exhibits a degree of hereditary and familial clustering, with approximately 10% to 20% of cases inherited and attributable to deleterious germline variants

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[5]. Individuals harboring pathogenic variants in some hereditary ovarian cancer susceptibility genes may also have an increased risk of other cancers, such as breast cancer (BC), endometrial cancer (EC) and so on. To date, many genetic susceptibility genes have been associated with OC [6, 7]. The most well-known genes are *BRCA1* and *BRCA2*, with the cumulative lifetime risk of OC for carriers of *BRCA1* and *BRCA2* germline pathogenic variants is approximately 54% and 32%, respectively [8]. Other genes involved in hereditary OC include homologous recombination repair (HRR) genes associated with hereditary breast and ovarian cancer (HBOC) syndrome, such as *RAD51 C, RAD51D, BRIP1,* and *PALB2*, as well as mismatch repair (MMR) genes associated with Lynch syndrome, including *MLH1, MSH2, MSH6*, and *PMS2* [7, 9]. Histologically, Lynch syndrome-associated OCs are primarily endometrioid and clear cell [10]. However, as much as 60% of OC familial risk remains unexplained [11], necessitating continuous efforts to discover new OC predisposition genes.

NGS enables simultaneous analysis of multiple genes associated with hereditary OC syndromes. It identifies rare germline variants of uncertain clinical significance and can uncover novel gene candidates in high-risk families, making it an effective tool for discovering predisposition genes in hereditary OC patients [12–16].

In this study, we applied WES to investigate the landscape of germline variants in a large cohort of consecutive Chinese women diagnosed with OC, thereby attempting to uncover novel pathogenic variants and cancer predisposition genes.

## Materials and Methods

### Patients

This study included 92 Chinese women diagnosed with OC who submitted blood samples for genomic sequencing between May 2020 and September 2023 at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. The clinical data and genetic test results were subjected to retrospective analysis. The study was approved by the ethics committee of the Run Run Shaw Hospital. All patients provided written informed consent to use their clinical information for research purposes.

### Whole exome sequencing

Genomic DNA (gDNA) was extracted from the peripheral blood of patient using the QIAamp DNA Blood Midi KIT (Qiagen, Germany) following standard protocols. WES of the patient was performed by DIAN Diagnostics Corporation (Hangzhou, China) using the IDT xGen Exome Research Panel v1.0 (Integrated DNA Technologies, USA) with a paired-end read length of 150 bp. Sequencing was performed using a NovaSeq 6000 system (Illumina, USA), with an average sequencing depth of 100 ×and an average coverage of 99.59%.

### Data analysis of whole exome sequencing

Bioinformatic processing and data analysis were performed after receiving the primary sequencing data. The sequences were aligned to the human reference genome hg19, and variants were called using the Genome Analysis Toolkit (GATK) [17] and annotated using VEP and Snpeff. Single nucleotide variants (SNVs) and indels were filtered and estimated via multiple databases, including NCBI dbSNP (https://www.ncbi.nlm.nih.gov/snp/), 1000 Genomes Project (https://www.internationalgenome.org/), Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org/), and in-house database (DIAN Diagnostics).

The analysis included 12 canonical OC predisposition genes (*ATM*、*BRCA1*、*BRCA2*、*BRIP1*、including *EPCAM* 3'deletion、*MLH1*、*MSH2*、*MSH6*、*PALB2*、*PMS2*、*RAD51 C*、*RAD51D*) in NCCN [18]. In addition, we annotated all genes in the WES data using the OMIM database (https://www.omim.org/), focusing particularly on genes related to tumors or cancers in the Clinical Synopses. We focused our attention on rare variants (minor allele frequency, MAF < 0,001). Missense variants were predicted by the REVEL (with scores > 0.75 is predicted to be damaging) and ClinPred (with scores > 0.5 is predicted to be damaging) and splice site variants by spliceAI. The pathogenicity of the variants was annotated with the ClinVar dataset (https://www.ncbi.nlm.nih.gov/clinvar), the Human Gene Mutation Database (HGMD), and Standards and Guidelines for the Interpretation of Sequence Variants of American College of Medical Genetics and Genomics (ACMG), which classified the variants into five categories: benign, likely benign, unknown significance, likely pathogenic, and pathogenic [19].

### Sanger sequencing

All pathogenic or likely pathogenic variants in 12 canonical OC predisposition genes were confirmed by Sanger sequencing. The specific PCR primers were designed with NCBI Primer-BLAST tool (https://www.ncbi.nlm.nih.gov/tools/primer-blast/). The PCR products were sequenced on ABI 3500Dx automated sequencer (Applied Biosystems, California).

### Statistical analysis

GraphPad Prism 5 software was used for the statistical analysis. Measurement data were analyzed using ANOVA. Count data were compared using the $\chi 2$ test. Differences among the three groups of samples were assessed: (a) pathogenic or likely pathogenic variants in

12 canonical ovarian cancer predisposition genes; (b) VUS in ovarian cancer predisposition genes or all variants in other predisposition genes; and (c) no mutations in any cancer predisposition genes. A p-value $<0.05$ was considered statistically significant.

## Results

### Clinical characteristics and genetic results in study population

Among the 92 patients, pathogenic or likely pathogenic variants in canonical OC predisposition genes were detected in 26 cases (28.26%, 26/92), while 24 cases (26.09%, 24/92) had VUS in canonical OC predisposition genes or all variants in putative predisposition genes only. No relevant variants were detected in 42 cases (45.65%, 42/92) (Table 1). A total of 62 mutations were detected among the 92 patients. The most deleterious mutations observed were in *BRCA1* (35%, 17/50), *BRCA2* (22%, 11/50), *RAD51D* (8%, 4/50), *ATM* (6%, 3/50), *BRIP1* (6%, 3/50) and *MLH1* (6%, 3/50) (Fig. 1).

The mean ages of the three groups were 55.12, 57.54, and 56.52 years, respectively, with no significant difference in age distribution ($P= 0.7395$). The proportions of patients reporting a first-degree relative with related malignancies (ovarian, breast, endometrial, prostate, colorectal cancers) were 23.08% (6/26), 4.16% (1/24), and 7.14% (3/42) in the three groups, respectively. The proportions of patients with concomitant related malignancies were 28.57% (8/26), 8.33% (2/24), and 2.38% (1/42) in the three groups, respectively. A family history of related malignancies ($P= 0.0027$) and a personal history of other malignancies ($P= 0.0009$) were considered features associated with hereditary OC.

Of the 26 patients with pathogenic or likely pathogenic variants, 25 had HGSC and 1 had CCC. Of the 24 patients with VUS, 17 had HGSC, 2 had LGSC, 4 had ENC, and 1 had CCC. The proportion of germline pathogenic cases among all HGSC was 38.71% (25/62), significantly higher than other histological subtypes ($P= 0.0024$).

### Spectrum of variants in canonical OC predisposition genes

Among the 12 canonical OC predisposition genes recommended by the NCCN, a total of 28 germline pathogenic or likely pathogenic variants were detected in 5 OC predisposition genes from 26 patients. These genes included HRR genes: *BRCA1* ($n= 13$), *BRCA2* ($n= 8$), *RAD51D* ($n= 4$), *BRIP1* ($n= 2$), and the MMR gene *MSH2* ($n= 1$). The findings are summarized in Table 2. All 25 patients carrying pathogenic variants in HRR genes had histological subtypes of HGSC. The patient harboring the *MSH2* variant had CCC and concurrent EC, suggesting Lynch syndrome.

Two patients (7.69%, 2/26) harbored two germline pathogenic or likely pathogenic variants in different genes, *BRCA1* and *BRIP1*, *BRCA1* and *BRCA2*, respectively. Additionally, 6 novel variants were identified,

**Table 1** Clinical Characteristics and genetic results of the Cohort

| Characteristic | Total ($n= 92$) | P/LP[a] ($n= 26$) | VUS[b] ($n= 24$) | no mutation[c] ($n= 42$) | *p*-value |
|---|---|---|---|---|---|
| **Age** | 56.39 | 55.12 | 57.54 | 56.52 | 0.7395 |
| **Histotypes** | | | | | 0.0024 |
| High-grade serous | 66 | 25 | 17 | 24 | |
| Low-grade serous | 4 | 0 | 2 | 2 | |
| Mucinous | 2 | 0 | 0 | 2 | |
| Endometrioid | 9 | 0 | 4 | 5 | |
| Clear cell | 7 | 1 | 1 | 5 | |
| Others[d] | 4 | 0 | 0 | 4 | |
| **Family history** | | | | | 0.0027 |
| Ovarian cancer | 4 | 3 | 0 | 1 | |
| Breast cancer | 2 | 2 | 0 | 0 | |
| Cervical cancer | 1 | 1 | 0 | 0 | |
| Colorectal cancer | 3 | 0 | 1 | 2 | |
| **Concurrent cancer** | | | | | 0.0009 |
| Breast cancer | 10 | 7 | 2 | 1 | |
| Endometrial cancer | 1 | 1 | 0 | 0 | |

[a] Pathogenic/likely pathogenic variants in 12 canonical ovarian cancer predisposition genes

[b] Variants of uncertain significance (VUS) in ovarian cancer predisposition genes or all variants in other predisposition genes only

[c] No mutation in all cancer predisposition genes

[d] Include 2 cases of teratoma, 1 cases of neuroendocrine tumors, and 1 case of ovarian sarcoma

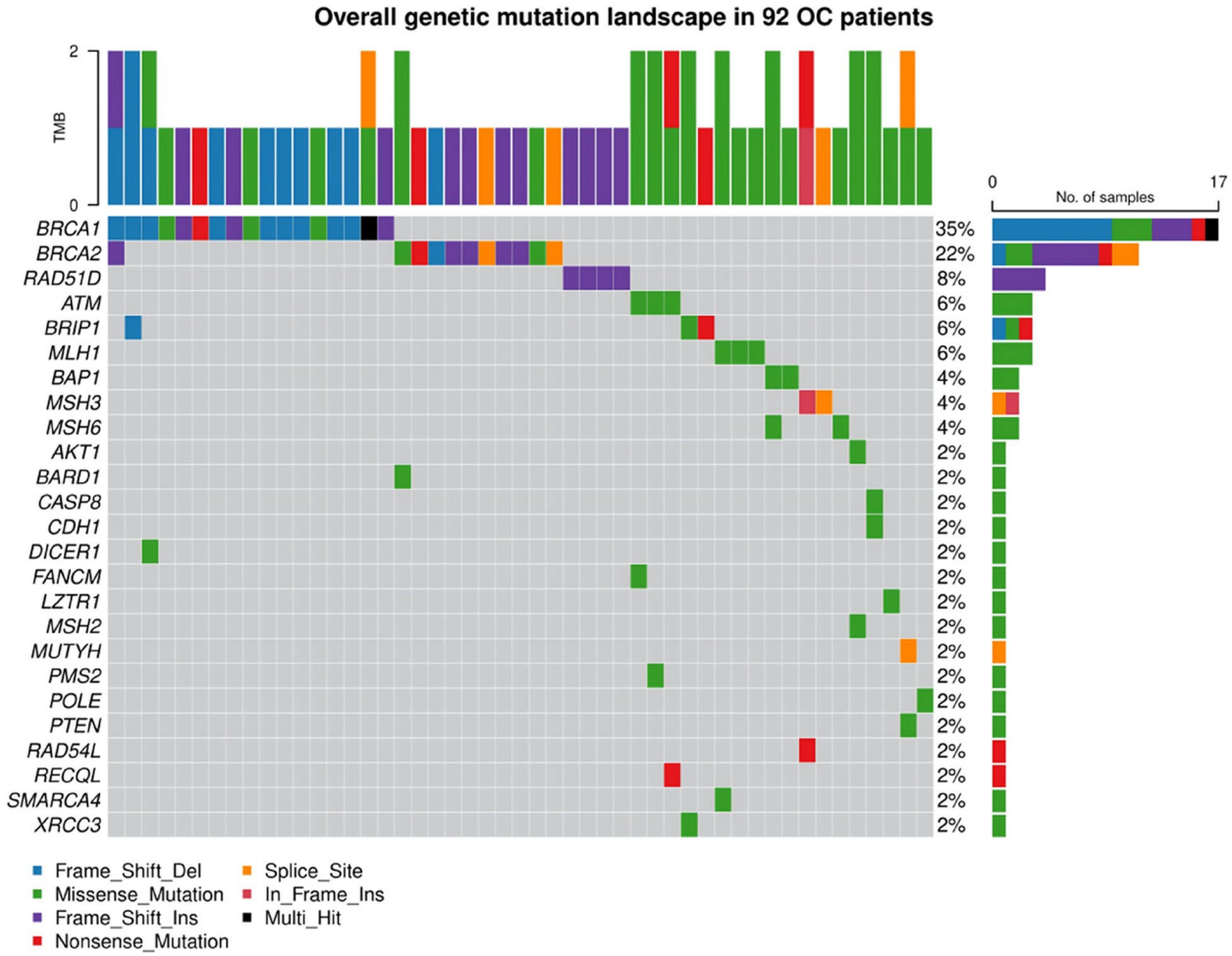


**Fig. 1** Over genetic mutation landscape in 92 OC patients

including NM_007294.4(*BRCA1*): c.4715_4740 del (p.Ser1572fs), NM_007294.4(*BRCA1*):c.3755 dup (p.Ser1253fs), NM_007294.4(*BRCA1*):c.2383 A > T (p.Lys795 Ter), NM_000059.4(*BRCA2*): c.5929 dup (p.Ile1977 AsnfsTer3), NM_000059.4 (*BRCA2*): c.5897 dup (p.His1966fs), and NM_032043.3 (*BRIP1*): c.3072 del (p.Ser1025HisfsTer34). Furthermore, the NM_002878.4(*RAD51D*): c.270_271 dup (p.Lys91IlefsTer13) was detected in four unrelated OC patients.

A total of 18 VUS were detected in 7 canonical OC predisposition genes, including *ATM* ($n = 3$), *BRCA1* ($n = 5$), *BRCA2* ($n = 3$), *BRIP1* ($n = 1$), *MLH1* ($n = 3$), *MSH6* ($n = 2$) and *PMS2* ($n = 1$) (Table S1). A patient carrying the *BRCA2* (NM_000059.4):c.6875 A > C (p.Glu2292 Ala) variant was diagnosed with OC and concurrent BC. Several tools predicted the variant to be damaging, in which, the REVEL score was 0.715 and the ClinPred score was 0.8974. This variant has been previously detected in patients with HBOC syndrome [20, 21].

#### Spectrum of variants in putative OC predisposition genes

A total of 16 variants were detected in 14 other proposed and novel familial cancer genes, including *BAP1* ($n = 2$), *BARD1* ($n = 1$), *CASP8* ($n = 1$), *CDH1* ($n = 1$), *FANCM* ($n = 1$), *LZTR1* ($n = 1$), *MSH3* ($n = 2$), *NBEAL1* ($n = 1$), *POLE* ($n = 1$), *PTEN* ($n = 1$), *RAD54L* ($n = 1$), *RECQL* ($n = 1$), *SMARCA4* ($n = 1$), and *XRCC3* ($n = 1$). There were 27 missense variants, 3 intronic variants, 1 in-frame insertion, and 3 nonsense variants (Table S2). Three loss of function variants were identified, which include NM_001142548.1 (*RAD54L*): c.1825 C > T (p.Arg609 Ter), NM_002907.3 (*RECQL*): c.796 C > T (p.Gln266 Ter), and NM_001114132.2 (*NBEAL1*):c.5837 dup (p.Tyr1946 Ter).

The case with the *RAD54L* variant(c.1825 C > T; p.Arg609 Ter) described a 64-year-old patient diagnosed with bilateral OC. The gnomAD does not include the

**Table 2** Spectrum of pathogenic or likely pathogenic variants in canonical OC predisposition genes

| Case | Age | Histotypes | gene | location | hgvsC | hgvsP | feature | ACMG |
|---|---|---|---|---|---|---|---|---|
| NH2309013 | 48 | HGSC | *BRCA1* | chr17:41,244,259–41,244,260 | c.3288_3289 del | p.Leu1098SerfsTer4 | frameshift | P |
| | | | *BRIP1* | chr17:59,761,335 | c.3072 del | p.Ser1025HisfsTer34 | frameshift | LP |
| NH200761 | 44 | HGSC | *BRCA1* | chr17:41,243,479–41,243,483 | c.4065_4068 delTCAA | p.Asn1355fs | frameshift | P |
| | | | *BRCA2* | chr13:32,913,558–32,913,559 | c.5073 dupA | p.Trp1692fs | frameshift | P |
| NH23081294 | 55 | HGSC | *BRCA1* | chr17:41,244,068–41244071 | c.3477_3480 del | p.Ile1159MetfsTer50 | frameshift | P |
| NH2303200 | 44 | HGSC | *BRCA1* | chr17:41,243,920 | c.3627 dup | p.Glu1210 ArgfsTer9 | frameshift | P |
| NH2210122 | 64 | HGSC | *BRCA1* | chr17:41,243,777–41,243,778 | c.3770_3771 del | p.Glu1257GlyfsTer9 | frameshift | P |
| NH2210037 | 56 | HGSC | *BRCA1* | chr17:41,245,352–41,245,355 | c.2193_2196 del | p.Glu732 ArgfsTer3 | frameshift | P |
| NH2203105 | 47 | HGSC | *BRCA1* | chr17:41,243,631–41,243,632 | c.3916_3917 del | p.Leu1306 AspfsTer23 | frameshift | P |
| NH2011103 | 52 | HGSC | *BRCA1* | chr17:41,245,586–41,245,587 | c.1961 delA | p.Lys654fs | frameshift | P |
| NH2010161 | 47 | HGSC | *BRCA1* | chr17:41,245,056–41245057 | c.2491 dupT | p.Tyr831fs | frameshift | P |
| NH2103146 | 53 | HGSC | *BRCA1* | chr17:41,223,190–41223216 | c.4715_4740 del | p.Ser1572fs | frameshift | LP |
| NH200659 | 58 | HGSC | *BRCA1* | chr17:41,243,792–41,243,793 | c.3755 dupT | p.Ser1253fs | frameshift | LP |
| NH200916 | 42 | HGSC | *BRCA1* | chr17:41,245,135–41,245,137 | c.2411_2412 delAG | p.Gln804fs | frameshift | P |
| NH200899 | 56 | HGSC | *BRCA1* | chr17:41,245,165 | c.2383 A > T | p.Lys795* | nonsense | LP |
| NH2209157 | 54 | HGSC | *BRCA2* | chr13:32,929,396 | c.7409 dup | p.Thr2471HisfsTer4 | frameshift | P |
| NH2202003 | 59 | HGSC | *BRCA2* | chr13:32,914,420 | c.5929 dup | p.Ile1977 AsnfsTer3 | frameshift | LP |
| NH2104049 | 64 | HGSC | *BRCA2* | chr13:32,893,467 | c.316 + 5G > C | | intronic | P |
| NH2012183 | 67 | HGSC | *BRCA2* | chr13:32,914,388–32,914,389 | c.5897 dupA | p.His1966fs | frameshift | LP |
| NH200999 | 66 | HGSC | *BRCA2* | chr13:32,914,587–32,914,588 | c.6096 dupT | p.Ile2033fs | frameshift | P |
| NH200775 | 53 | HGSC | *BRCA2* | chr13:32,914,284–32,914,289 | c.5792_5797 delinsCAAATTT | p.Gln1931fs | frameshift | P |
| NH200704 | 58 | HGSC | *BRCA2* | chr13:32,914,174 | c.5682 C > G | p.Tyr1894* | nonsense | P |
| NH23081291 | 60 | HGSC | *RAD51D* | chr17:33,434,458 | c.270_271 dup | p.Lys91IlefsTer13 | frameshift | P |
| NH23080321 | 60 | HGSC | *RAD51D* | chr17:33,434,458–33,434,458 | c.270_271 dup | p.Lys91IlefsTer13 | frameshift | P |
| NH20230423 | 70 | HGSC | *RAD51D* | chr17:33,434,458 | c.270_271 dup | p.Lys91IlefsTer13 | frameshift | P |
| NH2110087 | 54 | HGSC | *RAD51D* | chr17:33,434,458 | c.270_271 dupTA | p.Lys91fs | frameshift | P |
| NH230614107 | 60 | HGSC | *BRIP1* | chr17:59,876,486 | c.1315 C > T | p.Arg439 Ter | nonsense | P |
| NH2208063 | 42 | CCC | *MSH2* | chr2:47,703,575 | c.2075G > T | p.Gly692 Val | missense | LP |

*P* pathogenic, *LP* likely pathogenic

frequency of this variant in normal East Asian populations. The *RECQL* variant (c.277G > T; p.Gln266 Ter) was identified in a patient with highly differentiated endometrioid ovarian carcinoma diagnosed at 56 years, and this variant has previously been detected in several patients with breast or ovarian cancer [22, 23]. There was no family history of cancer associated with these two patients. The patient carrying the *NBEAL1*:c.5837 dup (p.Tyr1946 Ter) variant was diagnosed with both OC and BC at 63 years, in addition to having a family history of colorectal cancer in the father and esophageal cancer in the brother.

## Discussion

In this study, a more comprehensive analysis involved examining factors such as patient age, the histological subtype of OC, the family history of cancer, and concurrent cancers. Interestingly, this study found that age is not a relevant factor for hereditary OC. However, the presence of serous ovarian cancer, especially the high-grade subtype, a family history of related cancers, and concurrent cancer strongly suggest the presence of hereditary OC. This finding is consistent with previous studies on *BRCA1/2* related OC, with similar conclusions observed in different populations across Asia, Europe, and Australia [24–26]. This valuable information can assist in accurately stratifying OC patients to determine the necessity of genetic testing and counseling.

In the past, genetic testing for screening of patients presenting hereditary OC focused mainly on *BRCA1* and *BRCA2* genes. However, studies have shown that multigene panel or WES significantly improves the diagnostic rate [27–29]. Particularly, WES allows the simultaneous assessment of virtually an unlimited number of genes. There are relatively few cohorts of multi-gene dedicated to the study of hereditary OC, especially by WES [30, 15, 31]. Through WES analysis of 92 OC patients, we identified *BRCA1* as the most frequently mutated gene with a detection rate of 14.13%, followed by *BRCA2* at 8.7%.

The mutation frequency of *BRCA1* aligns with previous findings, while the observed *BRCA2* mutation frequency exceeds previously reported rates in both Asian and Western populations [6, 32, 33]. Additionally, *RAD51D* was identified as a gene with a relatively high number of variants, which may indicate the importance of genetic testing in OC patients. Furthermore, we identified five novel variants of *BRCA1/2* through WES, expanding the mutation spectrum of *BRCA1* and *BRCA2*.

Based on the unbiased nature of WES, we aimed to discover potential OC predisposition genes. We found loss of function variants in *RAD54L*, *RECQL,* and *NBEAL1* in OC patients. *RAD54L* is involved in DNA damage repair and belongs to the SNF2/SWI2 family, which has previously been identified as a potential causative gene for HBOC [34]. *RECQL* is involved in DNA double-strand break repair through nonhomologous end-joining and in telomere maintenance [35, 36], and is believed to be associated with premature ovarian failure. In addition to *RECQL*, heterozygous loss of function mutations within the *FANCM* gene were significantly associated with premature ovarian failure and HBOC risk [37]. *NBEAL1* encodes one of nine human BEACH domain-containing proteins (BDCPs). BDCPs play a role in molecular mechanisms including vesicular transport, apoptosis and receptor signaling [38]. The *NBEAL1*:c.5837 dup (p.Tyr1946 Ter) variant is located on beige and Chediak-Higashi domain (https://www.deciphergenomics.org/). Loss of function variants in the *NBEAL1* gene have previously been reported to be associated with hereditary BC [39].

Based on the above analysis, we consider *RAD54L*, *RECQL,* and *NBEAL1* as putative OC susceptibility genes. However, there is a lack of experimental research on the roles of *RAD54L*, *RECQL*, and *NBEAL1* in hereditary OC. The literature does not provide substantial evidence of an increased prevalence of these pathogenic variants in OC cases compared to healthy controls. Additionally, due to geographical and age limitations of the patients in our study, we were unable to obtain samples from their relatives for genetic testing to further evaluate these variants. Nevertheless, our findings suggest that these genes warrant special attention in future testing of hereditary OC. Once a sufficient number of patient samples have been accumulated, further assessment can be made regarding their relevance to hereditary OC.

Primarily, the generalizability of our findings is constrained by the homogeneous demographic characteristics of the cohort, which was exclusively composed of Chinese descendants. Furthermore, the limited sample size ($n = 92$) has precluded the robust detection of rare genetic variants, potentially compromising the statistical power for establishing definitive genotype–phenotype correlations. In the future, expanding the cohort through single-center or multi-center international collaborations is needed to enhance sample representativeness. Meanwhile, systematic functional research is needed for the unknown variants, which will facilitate the elucidation of pathogenic mechanisms underlying hereditary OC syndromes.

## Conclusions

In this cohort study of 92 OC patients subjected to WES, we identified clinically actionable pathogenic or likely pathogenic variants in 28.26% of cases. The present research not only confirms the importance of canonical predisposition genes recommended by the NCCN, but also reveals other potential predisposition genes, which require further investigation. WES significantly improved the detection rate of variations in OC patients, providing new insights into the genetic basis of OC. Our research emphasizes the correlation between family and personal cancer history with hereditary OC, supporting the importance of considering these factors in clinical management.

### Abbreviations

| | |
|---|---|
| NGS | Next-generation sequencing |
| OC | Ovarian cancer |
| WES | Whole exome sequencing |
| EOC | Epithelial ovarian cancer |
| HGSC | High-grade serous carcinoma |
| LGSC | Low-grade serous carcinoma |
| MC | Mucinous carcinoma |
| ENC | Endometrioid carcinoma |
| CCC | Clear cell carcinoma |
| BC | Breast cancer |
| EC | Endometrial cancer |
| HRR | Homologous recombination repair |
| HBOC | Hereditary breast and ovarian cancer |
| MMR | Mismatch repair |
| VUS | Variants of uncertain significance |
| NCCN | National Comprehensive Cancer Network |
| SNVs | Single nucleotide variants |
| gnomAD | Genome Aggregation Database |
| ACMG | American College of Medical Genetics and Genomics |
| BDCPs | BEACH domain-containing proteins |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14302-w.

Supplementary Material 1

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### Authors' contributions

XJG and SL conceived of the presented idea and supervised the findings of this work. XJG and XZ contributed to sample collection. FLZ developed the theory and performed the statistical analysis. FLZ and QYZ wrote the manuscript with support from LQ. HQ and XZ participated in major revision process. All authors discussed the results and contributed to the final manuscript.

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**Data availability**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated and/or analysed during the current study are available in the NCBI databases with the SRA accession number PRJNA1209716.

## Declarations

**Ethics approval and consent to participate**
The research adhered to the Helsinki Declaration and was approved by the ethics committee of the Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. All patients provided written informed consent to use their clinical information for research purposes. All experiments were performed in accordance with relevant guidelines and regulations.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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